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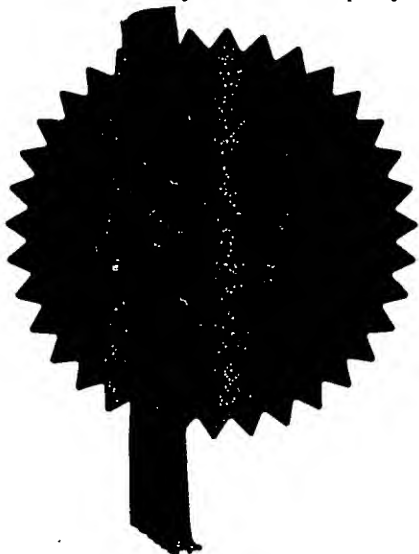
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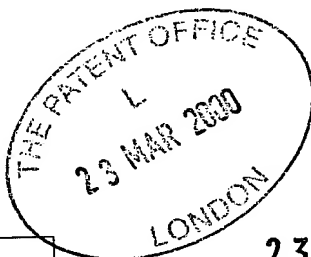


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Patent Act 1977

### 1 Title of invention

FORMULATION

- 1 Please give the title of the invention

### 2 Applicant's details

#### ☒ First or only applicant

- 2a If you are applying as a corporate body please give:

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PFIZER LIMITED

Country (and State of incorporation, if appropriate)  
UNITED KINGDOM

- 2b If you are applying as an individual or one of a partnership please give in full:

Surname  
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- 2c In all cases, please give the following details:

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5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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## 6

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7

The answer must be 'No' if:  
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Please supply duplicates of claim(s), abstract, description and drawing(s).

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## 8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)

Description  *M*

Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority document (please state how many)

Patents Form 7/77 - Statement of Inventorship and Right to Grant (please state how many)

Patents Form 9/77 - Preliminary Examination/Search

Patents Form 10/77 - Request for Substantive Examination

## 9 Request

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FORMULATION

This invention relates to new formulations of medicaments, especially in relation to oral health care, especially suitable for the treatment of non-human animals, especially companion animals  
5 such as dogs and cats.

The formulations may also be useful in the treatment of certain human subjects, e.g. those who may have difficulty in maintaining oral hygiene via conventional methods e.g. via oral  
10 brushing.

Administration of a medicament to the oral cavity of non-human animals, particularly via gels, paste, solution etc., especially for the purpose of oral health, is recognized to be difficult and inconvenient due to the need to maintain the animal's mouth open involuntarily for a prolonged  
15 period, to enable dosing. The problem may also be encountered in the human subject groups mentioned above.

Approaches to overcome this drawback relate principally to the use of mechanically robust chewable dosage forms including rawhide, dried foodstuff, natural and synthetic polymers impregnated with medicament, which can be offered to the animal for consumption, negating  
20 the need for invasive manipulation within the animal's mouth.

For example EP 0 272 968 and WO 94/05252 disclose chewable rawhide and dried foodstuff such as beef tendon or ligament which are impregnated with medicament, for example: sodium fluoride (anti-caries agent), sodium benzoate (anti-calculus agent) and bromochlorophene (anti-  
25 microbial agent), for use as oral health products for dogs and other domestic animals.

US-4,892,748 and EP 0 552 897 B1 disclose degradable chew matrices based on cellulosic fibrous material bound with a gum system such as methyl cellulose, to impart flexibility, wherein, the matrices may be incorporated with additives such as inorganic pyrophosphate  
30 salts, to control tartar.

US-5,683,722 discloses a dosage form for orally administering chemical or medicinal substances such as vitamins, trace elements, amino acids, nutritive substances etc., to domestic or wild animals, wherein the dosage form comprises a palatable hydrophobic outer shell and a  
35 porous water-soluble core impregnated with the drug.

In the above disclosed systems, the release of medicament occurs by a process of dissolution from the matrix as a result of prolonged and constant gnawing or chewing on the dosage form

to facilitate exposure in the oral cavity. Exposure of the medicament within the oral cavity is recognized to be discontinuous and variable as the animals do not generally gnaw or chew on the entire dosage form over a continuous interval to fully extract the medicament. The efficiency of dose delivery is therefore substantially imprecise and erratic, which can lead to poor therapeutic control and the potential for resistance development particularly with anti-microbial and anti-fungal therapies.

Unit dose chewing gum-based systems, as exemplified by US-5,736,175 and US-4,564,519 for human use, wherein the entire dosage form may be *consumed* within the oral cavity over a continuous interval, and wherein the chewed gum is later discarded, can overcome the discontinuity in release. Such systems however are not suitable for non-human animal use since the gum base cannot easily be voluntarily discarded, potentially giving rise to gastrointestinal obstruction via ingestion thereof. In addition, the chewing action of the animal cannot be voluntarily controlled as in the normal human situation to ensure rapid and complete release of the medicament from the dosage form.

Liquid-filled dosage forms are available commercially for human use, and are known as Locketts®, Halls®, etc., wherein the medicament, typically menthol, is contained in the liquid-filled centre encased by a stiff and brittle outer shell. The brittle nature of the outer shell renders it susceptible to *catastrophic* fracture (i.e., rapid crack propagation and branching) on mastication to release the medicament, which is then swallowed to relief sore throats and aid nasal congestion. The fracturing process gives rise to smaller fragments that can be swallowed directly or may require very limited mastication prior to swallowing. Whilst the release of medicament is rapid, the brittle nature of these systems do not lend themselves to prolonged mastication to enable the distribution of the medicament in the oral cavity to facilitate local oral exposure. The typical compressive Young's modulus values of the shell used in these systems are of the order of 20MPa, which is high and typically requires significant force to incur fracture.

US-4,428,927 discloses a masticatory soft elastic gelatine capsule, also based on the liquid-filled concept for the delivery of medicaments orally. The masticatory substance, as described in this invention however, is typically very soft, designed to promote rapid rupture and release of the inner fill, leaving just the outer shell, which can then be discarded.

Other prior arts include those disclosing human chewable medicated and confectionery products, such as Nicorette®, which contains nicotine, used to control smoking-dependency and Airwaves®, which contains menthol, used to freshen breath and clear the nasal passages.



The medicaments in these systems are either dispersed in the matrix of the base (Nicorette®) or are coated onto pellets which are then compressed into the final configuration (Airwaves®). The underlying material in both these systems is a gum base composite that is non-edible and thus is unsuitable for non-human animal use as the dosage form cannot be discarded as in the  
5 example described above.

There thus exists a need for an acceptable dosage form which enables more accurate and timely release of a unit dose of the medicament within the oral cavity, especially in relation to the subject groups mentioned above, and especially in relation to oral health medicaments suitable  
10 for non-human animal treatments.

According to the invention, there is provided a formulation for a medicament comprising:  
a solid masticable portion and one or more reservoir portions encompassed by said masticable portion;  
15 the solid masticable portion consisting of a fully edible material, having a Young's modulus of 0.01–5MPa and penetration forces in the range 0.07–180N,  
the reservoir portion or portions comprising a releasable unit dose of the medicament in a fluid (preferably a liquid) form, with a viscosity below 800mPa.s at body temperature (ca. 36–ca.40°C), and preferably between the range of 50–200mPa.s,  
20 such that on mastication, the masticable portion is ruptured and the unit dose of the medicament is released in a short space of time from the reservoir portion into the oral cavity.

The solid masticable portion consists of materials that are non-brittle, fully edible, which exhibit mechanical properties specifically tailored to encourage mastication in the oral cavity.  
25 The mechanical properties of the masticable portion can be described by two main parameters, i.e. the compressive Young's modulus and the force required to penetrate this portion.

The compressive Young's modulus (E) is taken to reflect the material's resistance to elastic deformation and may be expressed as the ratio of applied compressive stress to compressive strain (Ashby and Jones, 1980). This property is used here to quantify the *chewability*  
30 characteristics. For the formulations of this invention, the value for E is typically in the range of 0.01–5MPa and more preferably between the ranges of 0.1–2MPa. Measurement of this parameter is performed by compressing a cylindrical metallic plunger, 15.84mm (outer diameter), against the chew at a constant rate of 5mm.min<sup>-1</sup> until a load of 5N is reached.

35

The top and bottom penetration forces ( $F_t$  and  $F_b$ , respectively) for the masticable portion are taken to reflect the material's resistance to fracture. These values are derived directly from the

force-displacement graph of the penetration test. According to this invention, the penetration forces as represented by  $F_i$  and  $F_b$ , are typically in the range of 0.07-180N and more preferably between the ranges of 1-29N. This test involves the compression and penetration of a stainless steel probe, 1.6mm (outer diameter), through the chew at a constant speed of 30mm.min<sup>-1</sup>. The test is stopped once the probe has moved by 40mm, *i.e.* a distance significantly greater than the thickness of the instant chews being tested.

More specifically, the chew under test is rested on a metal block that contains a rectangular opening, 1cm wide, to accommodate the metal probe when it exits the chew. Initially, the probe makes contact and deforms the chew. At a maximum critical force,  $F_c$ , the probe breaks through the shell of the chew and starts penetrating the bulk. A second maximum, higher than the first one due to friction, is observed when the probe breaks through the bottom face of the shell. Similar tests have been reported in the literature of textural testing of gel systems (Baker, 1938; Szczesniak, 1975; Mitchell, 1976; Nakakura *et al.*, 1992), where only the top penetration force is measured. The advantage of the test described here is that it can be applied to composite or heterogeneous materials, for example, those containing mainly a solid material but interspersed with one or more portions of fluid.

"Edible" means can be ingested without causing subsequent gastrointestinal obstruction, discomfort or malfunction, preferably wholly digestible.

Examples of masticable portion materials include edible sugars (*i.e.*, polysaccharides) such as sucrose, glucose, mannose, maltose, etc., and/or polyols (*i.e.*, hydrogenated polysaccharides) such as xylitol, sorbitol, maltitol, maltotritol, etc., as the base with viscoelastic polymer additives such as starch, gelatine, gum arabic and cellulosic fibres to impart elasticity and toughness.

A polysaccharide and/or hydrogenated polysaccharide base is typically the dominant component of the masticable portion and will make up typically greater than about 50% of the total solid (TS) content by weight, and preferably greater than about 60% w/w, for example about 74% w/w.

The viscoelastic polymer additives such as gelatine and/or gum arabic, will make up less than 50% of the TS content of the masticable portion by weight, and preferably less than 30%, for example 14%.

The masticable portion may also include mucoadhesive additives to promote retention within the oral cavity, such as cellulose-based polymers for example, hydroxy propyl methyl cellulose

(methocel) and sodium carboxy methyl cellulose (Carbopol™). When present, these agents will make up typically less than 20% of the TS content of the masticable portion by weight. Flavourant and colourant may also be included in the masticable portion, and when present will make up less than 30% of the total solid content of the chewable portion by weight, and preferably less than 20%, for example 12%. Examples of flavourant include wood smoke, meat, liver powder, fish extracts, cheese, chocolate, fermentation products such as yeast and malt. Flavourants may be included as a single entity or in combination.

10 Preferably the masticable portion comprises consists of gelatine, edible gum (pref. arabic), polysaccahrides (e.g. sugars such as sucrose and/or glucose, e.g. in the form of glucose syrup), hydrogenated polysaccharides (e.g. sorbitol, xylitol, etc.) and/or inverted sugars. More preferably the masticable portion consists of an admixture of these such as "Lycasin®", (which comprises hydrogenated derivatives of partially hydrolysed starch, principally sorbitol and maltitol. The full specification for Lycasin® is described in Rockström, 1980 or from the  
15 commercial manufacturers: Roquette Frères (France) and Lycasin Starch Ltd (Sweden). A suitable grade of Lycasin® useful for the masticable portion is Lycasin 80/55®, which comprises mainly maltitol syrup. The full specification for Lycasin 80/55® is also described in Rockström, 1980.

20 During processing, the ingredients of the masticable layer may need to be heated or processed further to ensure the correct gelatinous properties of this portion (see above for properties). The temperature of this solution needs to be carefully controlled in the cooking chamber, preferably with the use of a continuous cooking systems operating under reduced pressure (a technique for cooking sugar mixtures which is well known in the art, Peters, 1989). The sources and models  
25 of typical industrial equipment to enable the processing are described in the pharmaceutical and confectionery literature, Peters, 1989.

The reservoir portion or portions comprises a solution or dispersion of a unit dose of the medicament either by itself (if suitable) or in a vehicle, with a viscosity of less than 800mPa.s  
30 at body temperature (~ 36-40°C), such that on mastication, the masticable portion is ruptured and the medicament can freely flow from the reservoir portion(s) into the oral cavity. Preferably >10 % of the reservoir portion is released after 10s chewing by a typical dog, such as a beagle.

35 Preferably the reservoir vehicle is water or an aqueous fluid.

Material for the fluid-filled reservoir portion or portions may include the medicament itself or the medicament solubilised or dispersed in a vehicle with the aforementioned properties. The total reservoir portion(s) will make up less than 60% of the total dosage form by volume, and preferably less than 30%, for example 20%.

5

Examples of aqueous reservoir vehicles include polysaccharides and/or polyol solutions for example sorbitol, glucose, high maltose, glycerol, syrups or preferably a mixture of some of these, for example "Lycasin® - preferably Lycasin 80/55®. The composition of these materials are as described above.

10

Suitable solutions of polymers may also be used to modify flow and viscosity characteristics, such as hydroxy propyl methyl cellulose (HPMC) solution, etc.. Examples of lipophilic (oil-like) reservoir vehicles include polyethylene glycol (PEG), polypropylene glycol (PG), edible oils such as olive oil, sun-flower oil, hydrogenated castor oil, palm kernel oil, sesame oil, etc.

15

Flavourant and colourant may also be included in the reservoir portion, and when present will make up less than 30% of the total volume content, and preferably less than 10%. Examples of flavourant include wood smoke, meat, liver powder, fish extracts, cheese, chocolate, fermentation products such as yeast extracts and malt.

20

Medicaments for local delivery to the oral cavity may include those pertinent for oral health such as those used to control/reduce plaque, to prevent/reduce halitosis, gingivitis, periodontitis and other periodontal infections.

25

Examples of these medicaments may include anti-bacterial agents, wherein the agents (their analogues and salts) are derived from bis-guanidino antibacterials such as chlorhexidine, hexetidine, alexidine, etc.; myxovirescin; cetyl pyridinium chloride; minocycline, doxycycline, chlortetracycline and other tetracycline antibacterials; anionic antibacterials such as triclosan etc.; nisin and other lantibiotics; malabaricone C and other argingipain inhibitors; ofloxacin and other quinolone antibacterials; sulfadiazine; actinobolin; histatins, bactenecin and other peptide antibacterials.

30

Further examples of these medicaments may include agents that have plaque anti-adherent properties, wherein the agents (their analogues and salts) are derived from morpholino-amino alcohols, such as delmopinol, octapinol etc., and other surface-active agents such as those derived from cationic and anionic surfactant classes.

35

Other examples of medicaments may also include antibacterial agents or antifungal agents used to treat infections of the oral cavity.

5 Other examples of medicaments may include agents that achieve systemic levels via sub-lingual or buccal absorption.

Other examples of medicaments may also include those used to prevent/treat systemic diseases such as antiparasitics, for example selamectin; antifungals, such as fluconazole and analogues; and others wherein the delivery route is via oral administration.

10 The invention provides scope for the delivery of medicaments in the solubilised form in the reservoir portion of the dosage form either to the gastrointestinal tract or locally to the oral cavity. One aspect of the invention is particularly useful for maximising the luminal exposure of lipophilic medicaments in animals (i.e., concentration within the gastrointestinal lumen),  
15 which is recognized to be limiting when the aqueous solubility of the medicament is low, typically less than 100µg/ml.

According to this invention, the ability to modify the nature of the reservoir vehicle, renders high flexibility in the choice of medicament which could be incorporated or solubilised into the  
20 dosage form as the release of the medicament occurs in the oral cavity. The medicament can be delivered in the oral cavity or along the gastrointestinal tract following ingestion.

Typical loading of the medicament in the reservoir portion can vary from 100%, where the medicament is in a suitable fluid form, to 0.001% (by weight/volume, or "w/v"), where the  
25 medicament is dispersed, solubilised. Where the medicament is dispersed and/or solubilised in the reservoir, the medicament typically forms 0.001 to 80%, preferably 0.01 to 20% w/v. Choice of medicament vehicle, concentration, etc. depends on factors such as the characteristics of the medicament, the size of the effect desired to achieve, the target subject group, etc.

30 The reservoir portion may contain further medicaments depending on the therapeutic need. When more than one medicament is present, the total drug loading in the reservoir portion is in the ranges mentioned above.

35 For oral health products, the speed of rupture and release of the medicament(s) from the reservoir portion is particularly pertinent. Typical rupture time to attain good coverage of the

teeth, gum and tongue areas is in the range 1 to 30 seconds, preferably 1- 10 seconds.  
Preferably >10% of the reservoir portion is released after this time, more preferably >50%.

5 Formulations of the invention are also especially useful for the oral delivery of medicaments that are poorly soluble, since the medicament can be solubilised in an appropriate vehicle of the reservoir portion and released along the gastrointestinal tract in a solubilised form. This negates the need for the medicament to undergo dissolution which may rate limit the overall oral absorption process. Medicaments which may benefit from this method of delivery include those with a partitioning coefficient ( $\log D$ ) >1 and aqueous solubility typically lower than 100 $\mu$ g/ml.

10 The dimensions of the dosage form disclosed in this invention can be specifically tailored to meet the particular needs of the application. Where the use is concerned with delivery of the medicament to the oral cavity, the dimensions should be such that the dosage form cannot be readily swallowed before mastication. Thus, whilst it is recognised that whilst the dimensions  
15 required to induce mastication is species size and variety dependent, the observation specific to this invention is that the dosage form should be typically above 10% of the volume of the oral cavity of that particular animal species.

The volume as described in the above context refers to the interior portion of the oral cavity  
20 enclosed within the jaw-line. This volume can be estimated using photographic methods or direct physical measurements of the jaw-line geometry.

In applications wherein local oral exposure is not pertinent, then there are no preferred range on the overall dimensions of the dosage form.

25 The dosage form as described in this invention can be of any shape as long as the entire dosage form can be accommodated into the oral cavity in a single administration. For processing reasons the preferred shapes include substantially hemispherical, cubic and ovoid. These configurations are designed to maximise the ratio of the reservoir portion to that of the overall  
30 dosage form by volume.

A preferred dosage form suitable for oral health care for domestic animals, e.g. dogs and cats, comprises the following (the percentages expressed are that of the total solid content of the relevant portion by weight):

35 a masticable portion containing gelatine (about 20%), gum arabic (about 3%) and flavourants: pork liver powder and beef powder, each at about 6%; in a hydrogenated polyssacharide Lycasin® base;

a reservoir portion comprising Lycasin®, malt flavouring (about 1%) by weight and the medicament (for example an oral health agent such as delmopinol at about 1-3% by weight);

A preferred dosage form shape is substantially hemispherical.

- 5 Preferably the reservoir will represent a maximum of 40% by volume of the final dosage form, more preferably 5 - 25% by volume.

The dosage form, as described here, can be prepared by any suitable process known to those skilled in such arts, including by a co-extrusion process wherein the masticable portion and  
10 reservoir portion are prepared separately and co-extruded to form a unit dose. The masticable portion forms the outer casing which encapsulates the inner reservoir portion. Unit doses of the co-extruded mass are dispensed accurately into a starch mould and dried over a period of 48 hours to allow the outer masticable portion to set.

- 15 The performance of the formulation, especially as related to local oral delivery, may be determined by measuring the level of exposure of the reservoir portion, pre-incorporated with a blue food dye, to quantify coverage within the oral cavity. Where the dosage form is chewed or gnawed by the animal then extensive coverage of the teeth, gum and tongue areas within the oral cavity may be achieved. This is particularly useful for application in oral health where the  
20 medicament is required to be distributed widely within the oral cavity for therapeutic efficacy.

We have found that the overall size of the dosage form is a pertinent parameter for promoting prolonged chewing and extended residence time in the oral cavity. Where the volume of the dosage form exceeds a critical percentage of the total volume of the animal's oral cavity, then  
25 the subject is forced to chew to render the dosage form into smaller-sized portions which can be swallowed without causing obstructions. Typically the dosage form volume is about 5-50% of that of the animal's oral cavity.

It is envisaged that a range of formulation sizes / shapes can be produced, adapted to the size  
30 and / or breed of animal concerned, as well as their therapeutic need. The formulation volume ranges, based on body weight, of a typical companion animal, such as a dog, is shown below:-

Dog body weight (kg)	Typical volume of formulation (cm <sup>3</sup> )
Up to 2	Up to 5
2.1-5	2 to 10
5.1 to 10	5 to 15
10.1 to 20	10 to 30
20.1 to 40	20 to 50

The invention is illustrated by the following examples.

Table 1 shows the level of coverage of the material emanating from the reservoir portion (using a blue dye) within the oral cavity following administration of the dosage form provided in Example 1.

5

The components of the formulation as shown in the formula according to Example 1, are expressed in terms of the percent total solid (TS) which forms the outer masticable portion, the percent by weight of the total dosage form and the mass per unit of dosage form. This method of formula expression is well known in art for fluid-filled dosage forms (Peters, 1989).

10

Example 1: Fluid-filled dosage form (sugar-based)

Components	% Total solid (TS) <sup>1</sup> content by weight	% Total dosage form by weight	g/unit
<b>Outer portion</b>			
Sucrose	46.35	29.80	7.233
Glucose syrup	27.65	17.78	4.315
Gelatine	14.00	9.00	2.184
Pork liver powder	6.00	3.86	0.936
Yeast extract	6.00	3.86	0.936
Water	N/A	18.12	4.396
<b>Reservoir portion</b>			
Lycasin 80/55®	N/A	17.23	4.180
Blue dye	N/A	0.34	0.084
<b>Total</b>		<b>100</b>	<b>24.264</b>

<sup>1</sup>TS – Total solid content of the outer portion of the dosage form

15 The gelatine was dissolved in 22.5mL of water in an appropriate glass vessel (e.g. 100ml Pyrex glass beaker), covered and then placed in a water bath at 55°C until a homogenous clear, yellow viscous solution was produced. The flavourants (pork liver powder and yeast extract) were then added to the gelatine solution, thoroughly mixed and stored at 55°C until required.

The sucrose and glucose syrup were weighed into a suitable cooking vessel (e.g., a 2-litre

20 Teflon coated pan), added with the remaining water and heated to between 115-130°C, preferably 123°C, with constant, gentle stirring and regular temperature monitoring. Once the target temperature was obtained, the cooking vessel was removed from the heat and the mixture cooled to ~ 90°C, with continuous stirring and regular temperature monitoring. The gelatine-flavour solution was then added and thoroughly stirred into the mixture to produce a

25 homogenous, viscous vehicle mixture. This vehicle mixture was then poured into the hopper of the co-depositor (Center in shell laboratory depositor PLC controlled, Supplied by: Werner Makat GmbH & Co.) designated for the outer shell. The hopper designated for the inner fluid-vehicle, was filled with the Lycasin® solution added with the blue dye, and maintained at 55°C.



The co-depositor was then used to deposit 16mL from the hopper designated for the outer shell, and 4mL from the hopper designated for the inner fluid-vehicle. The co-extruded mass was then left to set in pre-formed hemispherical starch impression moulds, constructed by imprinting solid wooden hemispherical blocks into the starch spaced 10cm apart, each corresponding to a volume of 20mL.

Once the masses had set in the mould (up to 48 hours), they were removed from the starch bed, dusted, wrapped in greaseproof paper and stored in air-tight plastic securitainer.

10

A formulation according to Example 1 was administered to a set of 8 dogs weighing in the range of 12-18kg and was chewed for greater than 20 seconds. At the end of this period the formulation was swallowed and the dog's oral cavity examined. The extent of coverage of the blue dye represents the area was as follows:-

15

Table 1:

Oral Tissues	Mean Percentage Coverage (by area as measured visually and by still digital photography)
premolar/molar teeth	80
upper gum margin	60
lower gum margin	60
incisors/canine teeth	50
tongue surface	95
throat	<5

20 This indicates that the dye was extensively distributed to all the areas within the oral cavity that are important targets for oral health. This is thus a measure of efficiency of delivery of reservoir material to the oral cavity.

25 Example 2: Fluid-filled dosage form (sugar-free base)

Components	% Total solid (TS) <sup>1</sup> content by weight	% Total dosage form by weight	g/unit
<b>Outer portion</b>			
Lycasin 80/55	65.00	41.74	10.143
Gelatine	20.00	2.84	3.121
Gum arabic	3.00	1.93	0.468
Pork liver powder	6.00	3.85	0.936
Beef powder	6.00	3.85	0.936

Water	N/A	18.09	4.396
<b>Reservoir portion</b>			
Lycasin 80/55®	N/A	17.04	4.140
Malt	N/A	0.17	0.040
Delmopinol	N/A	0.49	0.120
	<b>Total</b>	<b>100</b>	<b>24.300</b>

<sup>1</sup>TS – Total solid content of the outer portion of the dosage form

The formulation provided in the above example can be prepared using the method described previously in Example 1, replacing the sucrose and glucose syrup with Lycasin 80/55® and the dye with the medicament delmopinol.

Further Examples are made in the same way as described above for Example 1 and contain the following components:

#### 10 Masticable outer portion composition:

Identity	Gelatine (%TS)	Gum Arabic (%TS)	Pectin (%TS)	Lycasin 80/55® (%TS)	Water content
A	14.5	1.0	0.1	50.6	21.8
B	2.0	5.0	0.1	66.9	14.0
C	4.75	1.0	1.0	67.25	14.0
D	12.0	5.0	1.0	48.2	21.8
E	12.5	1.0	0.1	52.6	21.8
F	4.0	5.0	0.1	64.9	14.0
G	6.75	1.0	1.0	65.25	14.0
H	10.0	5.0	1.0	50.2	21.8
I	4.75	1.0	0.1	68.15	14.0
J	12.0	5.0	0.1	49.1	21.8
K	14.5	1.0	1.0	49.7	21.8
L	2.0	5.0	1.0	66.0	14.0
M	6.75	1.0	0.1	66.15	14.0
N	10.0	5.0	0.1	51.1	21.8
O	12.5	1.0	1.0	51.7	21.8
P	4.0	5.0	1.0	64.0	14.0
Q	12.5	3.0	0.5	50.2	21.8

The outer masticable portion also contains flavouring (e.g. pork liver flavouring) at 12%TS

#### Reservoir Portion

##### 15 (A) Vehicle fills:

- 1 Lycasin 80/55®
- 2 Glucose syrup
- 2 PEG 300
- 20 3 PEG 600

The reservoir also contains malt flavouring at 8%.

**(B) Drug concentrations:**

delmopinol at 1%w/v, 2%w/v and 3%w/v  
octapinol at 1%w/v, 2%w/v and 3%w/v

5

Variations to produce more Examples are made by:

- using the same masticable layer components mentioned above, substituting the flavouring for another flavour, such as will be acceptable to whichever species of animal is to be treated;
- 10 using the same reservoir components mentioned above, substituting the flavouring for another flavour, such as will be acceptable to whichever species of animal is to be treated;
- using the same reservoir components mentioned above, substituting the medicament for another medicament or medicaments, such as are suitable for the treatment of the specific condition to be treated, such as those specifically mentioned above, and to whichever species,
- 15 size, etc. of animal is to be treated (including variation of the dosages as appropriate); and variation of the size of the final formulation to suit the size of oral cavity of whichever species is to be treated;

- The formulations described above may be deposited into any shapes, sizes etc., pre-formed in starch moulds as described above.
- 20

It is of course to be recognised that multitudinous other variations of the Examples mentioned herein are included within the spirit of the invention.

- 25 All references mentioned herein are incorporated in their entirety.

Where "treatment" is mentioned, it is to be understood as including preventative treatment as well as alleviation and cure of medical conditions.

30

**References**

- Ashby, M.F. and Jones, D.R.H. (1980) *Engineering Materials 1 – An introduction to the their properties and applications*, Pergamon Press, Exeter, pp. 29-35
- 35 Baker, G.L. (1938) Improved Delaware jelly strength tester. *Fruit Products J.* 17 (11), pp. 329-330.
- Mitchell, J.R. (1976). Rheology of gels (review paper). *J. Texture Studies* 7, pp. 313-339
- Nakakura, H., Nishigaki, F., Sambuichi, M., Miura, Y. and Osasa, K. (1992) Studies on mechanical compression properties of gels. *Nippon Shokuhin Kogyo Gakkaishi* 39 (1), pp. 8-15
- 40

- Peters, D. (1989) in *Pharmaceutical Dosage forms: Tablets*, Ed. Liberman, H., Lachman, L., and Schwartz, J., Marcel Dekker, New York, pp. 497-500
- Rockström, E. (1980). Lycasin hydrogenated hydrosylates, in *carbohydrates sweeteners in food and nutrition*, Academic Press, New York, pp. 225-232
- 5 Szczesniak, A.S. (1975) Textural characterization of temperature sensitive foods. *J. Texture Studies* 6, pp. 139-156

It will be understood that what will be claimed will include:

- (1) a formulation for a medicament or combination of medicaments comprising:  
a solid masticable portion and one or more reservoir portions encompassed by said solid masticable portion;  
5 the solid masticable portion consisting of a fully edible material, having a Young's modulus of 0.01–5MPa and penetration forces in the range 0.07-180N,  
the reservoir portion or portions comprising a releasable unit dose of the medicament in a fluid (preferably a liquid) form, with a viscosity below 800mPa.s at body temperature (ca. 36-  
ca.40°C),  
10 such that on mastication, the masticable portion is ruptured and the unit dose of the medicament is released in a short space of time from the reservoir portion into the oral cavity;
- (2) a method of treatment of a human or non-human animal subject in need of such treatment comprising administration of a formulation according to (1) above;  
15
- (3) some specific formulations mentioned herein.

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